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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/767,374	01/29/2004	Avi Ashkenazi	P1216R1C1D1	4761

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HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/767,374	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52,54,55 and 57-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52,54,55 and 57-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/19/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. Claims 52, 54-55 and 57-59 are pending and under examination.

2. The specification on page 1, should be amended to reflect the status of parent applications 09/953,499 and 09/254,465.

2. Applicant's IDS, filed 4/19/05, is acknowledged.

3. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

4. Claims 52, 54-55 and 57-59 are rejected to under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons of the record.

Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

The claims are directed to isolated polypeptides of SEQ ID NO: 2 referred to in the specification as PRO362 encoded by polynucleotides. The instant application does not disclose the biological role of the PRO362 polypeptide or its significance. The instant specification asserts specific utilities for the claimed invention, for the treatment of conditions characterized by inflammation associated antigens (pages 1, lines 10-15 in particular). The specification also asserts that the claimed PRO362 is a member of the immunoglobulin superfamily known as Junctional Adhesion Molecule (JAM). JAM is acknowledged by the Applicants to inhibit spontaneous and chemokine-induced monocyte transmigration through and endothelial cell monolyayer in vitro (see page 2, lines 8-14). Base on PRO362 homology to JAM, Applicant asserts that the compounds of the invention are expressed in elevated levels in or otherwise associated with human diseases such as inflammatory bowel disease, other inflammatory diseases of the gut as well as colorectal carcinoma (see page 2, lines 15-20). The specification asserts that the proteins of the invention are useful for diagnosis and/or treatment (including prevention) of immune related diseases (see page 3, lines 16-18). The specification asserts that it is contemplated that the polypeptides, antibodies and other active compounds of the present invention may be used to treat various inflammatory diseases and conditions, such as T cell mediated diseases, including those characterized by infiltration of leucocyte cells into a tissue, stimulation of T-cell proliferation, inhibition of T-cell proliferation, increased or decreased vascular permeability or the inhibition thereof (see page 42, lines 17-20).

These utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for PRO362. The disclosed polypeptide is said to have a potential function based upon its amino acid sequence similarity

(unspecified) to other known proteins, i.e., JAM. After further research, specific and substantial utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

The instant situation is directly analogous to that which was addressed in *Brenner V. Manson*, 148 U.S. P. Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this borad interpretation was not the intended definition of "useful" as it appears in 35 U.S. C. § 101, which requires that an invention must have either an immediatedly apparent or fully disclosed "real world" utility. The instant claims are drawn to a polypeptide of as yet undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the PRO362 of the instant application was, as of the filling date, useful to treat various inflammatory diseases and conditions, such as T cell mediated diseases, including those characterized by infiltration of leucocyte cells into a tissue, stimulation of T-cell proliferation, inhibition of T-cell proliferation, increased or decreased vascular permeability or the inhibition thereof as stated on page 42, lines 16-20 of the specification. Until some actual and specific significance can be attributed to the protein identified in the specification as PRO362, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or "real world" utility as of the filing date.

Based on the MLR reaction, Applicant asserts that either "Compounds which stimulate proliferation of lymphocytes are useful therapeutically where enhancement of an immune response is beneficial..." or "Compounds which inhibit proliferation of lymphocytes are useful therapeutically where suppression of an immune response is beneficial." See Example 5, on page 54, lines 1-9. This is not a substantial utility because there is no information regarding the correlation of the MLR results to any real-life diseases. There is no information regarding what subsets of immune responses, immune cell types etc., are targeted by compounds with activities in MLRs. This was considered comparable to the leukokine example in the guidelines, where membership in a general class does not provide information regarding a use/function for this one.

Applicant asserts at page 54, Example 5 of the specification provides stimulatory activity in a mixed lymphocyte reaction (MLR) assay. However, the ability of a protein to stimulate lymphocyte proliferation in this assay does not support a specific and substantial utility for the claimed invention. The ability to stimulate or inhibit lymphocyte proliferation in the MLR assay is an artificial *in vitro* system and does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function. The assertion that the claimed invention could be useful for the treatment of conditions where enhancement of the inflammatory response would be beneficial (page 3, lines 8-10 and Example 5) is not specific since there are many such conditions, and it is not predictable of which conditions the claimed

invention may function, if any.

Mixed lymphocyte culture (MLC) is a special case of antigen stimulation in which T lymphocytes respond to foreign histocompatibility antigen on unrelated lymphocytes or monocytes. MLC is a functional assay of cellular response to stimulatory determinants associated predominantly with HLA class II molecules. A single genetic locus or region, known as HLA, controls the MLC reactivity. The MLC assay recognizes disparate HLA class II molecules and the resulting T-cell activation, which is thought to represent an *in vitro* model of the afferent arm of the *in vivo* allograft reaction. The degree of reactivity observed correlates with the degree of antigenic disparity between responding and stimulating cells. Briefly, when the lymphocytes of 2 HLA-disparate individuals are combined in tissue culture, the cells enlarge, synthesize DNA, and proliferate, whereas HLA-identical cells remain quiescent. Since both cells will normally proliferate, a one way test is used to monitor the response of a single responder cell by inactivating the stimulator cell by radiation or drugs in order to inhibit DNA synthesis of the stimulator cell. The proliferation is driven primarily by the differences in the class II HLA antigens between the 2 test cells (or individuals). This reaction is not predictive of general responses of the immune system because, *in vivo*, activation of a lymphocyte is controlled not only by antigen binding but also by interactions with other cells. All T cells must cooperate with antigen-presenting cells, whereas B cells and cytotoxic T cells depend on helper T lymphocytes. These interactions either require direct surface-to surface contact or are mediated by cytokines that act only over extremely short distances. Because of this interdependence, lymphocyte activation occurs commonly and efficiently in the secondary lymphoid organs, where lymphocytes, antigens, and antigen-presenting cells encounter one another at close quarters. See pages 30-31, 208-209, 246-247 of "Basic and Clinical Immunology," 1994. See also, "Manual of Clinical Laboratory Immunology," 6th Edition at pages 1164-1166.

Kahan clearly states that no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from *in vitro* systems to *in vivo* conditions (Cur. Opin. Immunol. 4: 553-560, 1992; see entire document, particularly page 558, column 2). Piccotti et al. (Transplantation 67: 1453-1460, 1999) demonstrate that IL-12 enhances alloantigen-specific immune function as determined by MLC, but this result in vitro does not result in a measurable response *in vivo* (i.e. failure to accelerate allograft rejection) (see page 1459). Campo et al. (Biological Trace Element Res. 79: 15-22, 2001) demonstrate that while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation *in vitro* nor produce immunosuppressive effects *in vivo*. Therefore, the MLC assay, which is art recognized for determining histocompatibility, does not appear to be predictive of general immune responses *in vivo*.

Additionally, difficulties arise in quantification when using MLC as a test for T cell function due to variations in stimulator cell antigens that determine the degree of genetic disparity between stimulator and responder cells. MLC is typically used for determining histocompatibilty in an individual and as a test for immunocompetence of T cells in patients with immunodeficiency

disorders. When running the MLC assay for determining histocompatibility for transplantation, autologous controls combining self with irradiated self are necessary to normalize the response of each cell to stimulators. Furthermore, there is known inherent variability of individual cellular responses from day to day which requires performing the entire familial MLC at one time in the case of determining histocompatibility for transplantation (page 246 in "Basic and Clinical Immunlogy"). When performing the MLC assay, each individual lot of a serum source should be screened for growth support capabilities and possible HLA antibodies (see page 1165 in "Manual of Clinical Laboratory Immunology"). Additionally, the screen should include a control response to a pool of allogeneic cells to measure maximum response and an autologous control to ensure low backgrounds.

Therefore, the MLC (a.k.a. MLR) assay is a measure of alloreactivity of one individual to another individual, rather than a general measure of immune function. This reactivity is governed by the antigenic disparity between the two individuals which are being compared in the assay. Depending on the individuals being tested, the MLC may indicate stimulation if they are HLA-disparate or the MLC may indicate no stimulation if the individuals are HLA-identical. The ability of the claimed invention to stimulate proliferation in the MLC assay may not be a general stimulus to lymphocyte proliferation, but rather a reaction to one of the MHC antigens on the responder cell. The instant specification fails to provide sufficient detail of the assay which was performed and fails to provide any data whatsoever in order for one of ordinary skill in the art to evaluate the conclusion that lymphocyte proliferation was stimulated by the claimed invention. As pointed out above, there are several controls which the art recognizes as being essential for meaningful results for this assay, including autologous controls, a control to determine maximum response, screening for possible HLA antibodies and growth support capabilities. Furthermore, there is known inherent variability of individual cellular responses from day to day, which would clearly dictate the need for internal controls. The specification indicates that CD4-IgG was used as a control, but it is not clear how this would control for background stimulation or provide for a measure of maximal stimulation. In conclusion, the results of the MLC (a.k.a. MLR) assay do not support a specific and substantial utility for the claimed invention because the assay is not predictive of immune response in general, and one of ordinary skill in the art would not expect a stimulatory effect in the MLC assay to correlate to a general stimulatory effect on the immune system, absent evidence to the contrary.

Example 6, Inflammatory cell infiltrates into guinea pig Skin, does not provide the skilled artisan with guidance for how to use the claimed PRO362 polypeptides. In Example 6, a sample of purified polypeptide is injected intradermally into the backs of hairless guinea pigs. The resulting blemishes at the injection sites are measured, and the injection sites are subjected to histopathological analysis to detect infiltration of inflammatory cells. Injection sites with visible inflammatory cells (including neutrophilic, eosinophilic, monocytic or lymphocytic cells) are scored positive. However, the skilled artisan would conclude that a positive result in this assay indicates that the polypeptide is capable of inducing a hypersensitivity response, which is a non-specific response of the immune system to a substance recognized as toxic. Please see attached Barsoum et al. (1997, Journal of Antimicrobial Chemotherapy 40 :721-724) who induce a hypersensitivity response in mice in a similar way to that done in instant example 5(p. 722,

"Delayed-type hypersensitivity assay"). In general, it is clear from the reference that such a response is not beneficial to the animal, as it indicates toxicity of the injected compound. Similarly, Szalai et al. (2000, Journal of Immunology 164:463-468) describe the Arthus reaction in guinea pigs using essentially the same assay as described in instant example 6 (p. 464, "Arthus reactions" and "Histology"). Again, the authors clearly indicate that a positive reaction in the assay indicates that the injected substance is an irritant, or is toxic. Thus, a positive result in instant example 6 indicates that the polypeptide is toxic. This information does not guide the skilled artisan as to how to use the claimed polypeptides. Example appears to be nothing more than a toxicity test and does not provide a real-world, readily available use.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 52, 54-55 and 57-59 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Further, besides an isolated polypeptide comprising SEQ ID NO: 2 encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209620, and the polypeptide consisting of the amino acid sequence from amino acid position 1 to amino acid position X of SEQ ID NO: 2, wherein X is any amino acid from position 271 to position 280, the specification fails to provide any guidance as to how to make any isolated polypeptide "having at least 95% amino acid sequence identity" to the amino acid sequence of the polypeptide of SEQ ID NO: 2 in claim 52(a), the amino acid sequence from amino acid position 1 to amino acid position X of SEQ ID NO: 2, wherein X is any amino acid from position 271 to position 280 in claim 52(b) or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209620 in claim 52(c); where said polypeptide molecule stimulates the proliferation of T lymphocytes in claim 52. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action mailed 7/30/04.

Applicant's arguments, filed 6/12/05, have been fully considered, but have not been found convincing.

Applicant submits that the test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation. Applicant contends that the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue. The mere fact that an extended period of

experimentation is necessary does not make such experimentation undue. Applicant further submits that it is well settled that patent Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of skill how to make and use the invention as broadly as it is claimed. In particular, Applicants argue the do not make "functional assignments based on sequence similarity", nor do they guess or require the skilled artisan to guess the function of the structurally related protein (variant PRO362). Instead, Applicants clearly teach making and identifying PRO362 sequence variants and testing of these variants in the functional MLR assay, without undue experimentation. Applicants conclude that this rejection, based on the teachings of Attwood, and Skolnick, is improper, because no prediction or guessing of function for variant PRO362 sequences is needed to practice the instant invention within the full scope of the claims currently pending.

However, the specification on page 42, lines 24-33, assign the claimed PRO362 polypeptides to the IGSF know as JAM based on sequence homology. Further, contrary to Applicant assertions, the specification on page 12, lines 24-33 defined "PRO362 variant" as an active PRO362 polypeptide as defined below having at least about 80% amino acid sequence identity with the PRO362 polypeptide having the deduced amino acid sequence shown in FIG. 3 (SEQ ID NO: 2) for a full-length native sequence PRO362 polypeptide. Such PRO362 polypeptide variants include, for instance, PRO362 polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the sequence of FIG. 3 (SEQ ID NO: 2). Thus, the claim 95% variant of SEQ ID NO: 2 are not limited to the naturally occurring polypeptide but include amino acids substitution, deletion and addition. Furthermore, there is tremendous variability in the importance of individual amino acids in protein sequences. Since the extracellular and the intrachain disulfide loops of the V-type domain is a key determinants of activity of PRO362 polypeptide, residue substitutions that are conservative (e.g., Glu in equilibrium Asp, Asn in equilibrium Asp, Ile in equilibrium Leu, Lys in equilibrium Arg and Ala in equilibrium Gly) can have severe phenotypic effects. There is no simple way to infer the likely effect of an amino acid substitution on the basis of sequence information alone. Therefore, one skill in the art would not be able to predicted what residue substitutions can replace and the polypeptide still have the claimed function.

The claims fail to meet the enablement requirement for the "how to make and use" prongs of the U.S.C 112, 1st paragraph. The instant fact pattern fails to indicate that a representative number of structurally related PRO362 polypeptide is disclosed. The artisan would not know the identity of a reasonable number of representative PRO362 falling within the scope of the instant claim and consequently would not have known how to make them. In order to satisfy 112, first paragraph, the specification has to teach how to make and use the polypeptides of the invention not how to identify the invention.

Applicant further argues that the specification describes methods of making polypeptide variants (page 20, lines 1) along with tools for determining the % identity between two amino acid sequences. Applicant concludes that one of ordinary skill in the art, based on the disclosure

provided in the specification and general knowledge in the art at the time the invention was made, can readily make a pRO362 variant and determine whether the variant falls structurally within the scope of claim 52. Applicant further contends that once it has been determined that a sequence is structurally within the scope of these claims, a skilled artisan is able to determine whether any given variant possesses the ability to stimulate the proliferation of T-lymphocytes, using the assay described in Example 5, which was also well known in the art at the time the invention was made. Applicant contends that there is nothing in the Examiner's arguments or otherwise of record that would indicate that more than routine experimentation would be required to make and use the polypeptides claimed.

Applicant is relying upon certain biological activities and the disclosure of a single species to support an entire genus. The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, the enablement issues of making the protein still remain because the specification does not teach and provide sufficient guidance as to which amino acid of SEQ ID NO:2 would have been altered such that the resultant polypeptide would have retained the function of stimulating the proliferation of T lymphocytes. In addition, variation up to 5% of SEQ ID NO: 2 (16^{20}) ~1.208925819 X 10^{24} PRO362 polypeptide variants provide a range of activities, not all which are necessarily predictive of the proliferation of T lymphoctes. Therefore, absent the ability to predict which of these polypeptides would function as claimed, and given the lack of data on regions critical for activity, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 7, 2005

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600

Gary C. Elliott
DIRECTOR
TC 1600

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600